Phase II Trial of R-837A for Previously Treated Patients with Advanced Squamous Cell Carcinoma[[1]](#endnote-1)

1Linda Taylor, 1Jose Ramirez, 1David Johnson, 1Michelle Garber, 1Mary Wingate

1Center for Conquering Cancer, San Antonio, Texas.

Address reprint requests to Linda Taylor MD PhD, Center for Conquering Cancer, San Antonio, Texas 78231. ltaylor@conqca.com

ABSTRACT

*Purpose*: To evaluate the efficacy and safety of R-837A (imiquimod [R837A]; Generic Pharma, Dallas, Texas) in two doses and placebo, a colloid infusion of a small synthetic antiviral molecule, in patients with pretreated advanced squamous cell carcinoma.

*Patient and Methods*: This was a randomized, single-blind, parallel-group, single center phase II trial. Two hundred ten patients with advanced SCC who were previously treated with one or two chemotherapy regimens were randomized to receive either placebo, 25cc, or 50cc.

*Results:* Efficacy was dependent on the dose of R-837A. The higher dose (0.50cc) was led to a reduction in the average number of tumors by 0.9 versus 1.4 on 0.25cc and 1.8 on placebo, with a *p-value* of 0.001. R-837A is also associated (*p-value* = 0.000) with reduced size of primary tumor by an average of 0.9mm for 0.50cc group and 0.6mm for the 0.25cc group, while those on placebo saw tumor group of 0.6mm on average.

*Conclusions:*  R-837A effectively treated intractable and advanced cases of squamous cell cancer in these patients. At 25cc, patients had a favorable profile with few side effects, at 50cc, patients experienced greater side effects but also reduced number and size of tumors. R-837A is an important, novel treatment option for patients with pretreated advanced SCC.

Squamous cell carcinoma is the second most common form of skin cancer. It is an uncontrolled growth of abnormal cells arising in the squamous cells, which compose the epidermis. An estimated 700,000 cases of squamous cell carcinoma (SCC) are diagnosed worldwide each year and approximately 2,500 people die from this condition.[1](#_ENREF_1) In the U.S., there are roughly 40,000 new cases each year. Head and neck cancer accounts for two percent of all cancer deaths.[2](#_ENREF_2) These cancers often present as a lump or sore.[2](#_ENREF_2) Other symptoms can include changes in the gums, blocked sinuses, swelling in the chin and jawbone, ear pain, pain in the neck or throat that does not go away.[2](#_ENREF_2)

Frontline therapies for this disease when caught early include Mohs Micrgraphic surgery, excisional surgery, Curettage and electrodessication, cryosurgery, radiation, photodynamic therapy, laser surgery, and topical medications such as 5-fluorouracil (5-FU) and imiquimod. This cancer usually remains confined to the epidermis for some time. However, if ignored, these tumors grow, necessitating more treatment. Eventually, the tumors will penetrate the underlying tissue which can lead to disfigurement of the head and neck. Three year, disease-free survival rates range from 40 to 50 percent with N1 disease, and 26 to 38 percent with N2 and N3.[3](#_ENREF_3)

In a small percentage (2 to 10 percent) SCC metastasizes to distant tissues and organs, creating a life-threatening situation.1 Concomitant non-oral cancers are found to be a poor variable for prognosis prediction.[4](#_ENREF_4) The survival rate for an individual with metastasized advanced SCC of the neck is less than 15 percent.[5](#_ENREF_5) It is important to realistically manage the patient’s and the family’s expectations if they should pursue radical treatment.

In a previous trial, the principal investigator published the results of a study which demonstrated the safety and R-837A in a sample of 30 treated rats. Eighteen of the treated rats lived on average thirty percent longer than to a control group of 20 rats.[6](#_ENREF_6) In that study, 90 rats were entered into the trial, 65 were given R-837A to test its safety and efficacy in treating induced cancers in the rats, and 25 served as controls. Thirty-seven of the rats did not finish the trial, thus their data was excluded. Reasons for not finishing included intense suffering in the animal, death—from the underlying disease we hypothesized—and in one case, the rodent escaped from the laboratory. In the study group, 5 of the surviving rats received a high dose of .1cc and the rest received .05cc of R-837A.

This study will evaluate whether R-837 given at two dosages: 20cc and 50cc is effective in reducing the number of tumors and the size of the tumors compared with a placebo control group. A secondary aim of the study is to evaluate the effectiveness of dosage with the expectation that the 50cc dosage will result in significantly reduced tumor size and number compared with the 20cc and placebo groups. No significant difference is expected in reported side effects between the two dosage groups.

Methodology

*DESIGN*

This multicenter study used a randomized, single-blind, placebo-controlled, parallel group, graded-dose design to evaluate the efficacy and safety of R-837A in 2 dose ranges. The study timeline included a baseline evaluation, a 6 week treatment period, and a post-study evaluation. The maximum duration was 8 weeks.

This study was approved by the Ethical Committees or Institutional Review Boards at each study site.

*INCLUSION AND EXCLUSION CRITERIA*

Adult patients were eligible for the study if they had a stage 4 squamous cell cancer of the head and neck that has not responded—defined as remission--to at least two rounds of FDA approved chemotherapy and/or radiotherapy (topic medications, simple excision, Mohs surgery, laser therapy, freezing, radiation therapy, or chemotherapy (imiquimod, 5-fluorouracil), or who wished to avoid disfiguring surgery.

Anyone who had not had at least two rounds of traditional treatment were not eligible. Patients were excluded from the study if they had major psychiatric (defined as major depression for more than three months, schizophrena, or (DSM IV codes of 293, 294, 295, 296, 300, or 301), or cardiovascular disorder, significant renal or hepatic impairment, or if they were pregnant, lactating or not using adequate contraception. Five hundred sixty seven potential subjects were screened for this study, 210 were selected. Patients who were pursuing other cancer treatment or nontraditional therapy were also excluded.

*PROCEDURES*

Researchers completed IRB Form K, and screened records in Sunrise for individuals who had undergone treatment for squamous cell carcinoma in the last year. The treating oncologist of record was contacted by the research staff and their assent requested to contact potentially eligible patients. Those patients were then asked to attend a screening and informational session. Of the 567 initially screened potential subjects, 7 were already deceased,123 had physicians who refused to permit participation, 91 refused screening, and 136 did not qualify after screening. At the screening visit, written informed consent was obtained. The history and records were reviewed and patients were examined via a physical exam (including height, weight, heart sounds, pulse, blood pressure), blood draw and MRI scan . Laboratory testing was reviewed and additional testing was done if needed.

Those patients who continued to meet inclusion and exclusion criteria were then randomized using a computer block approach to one of the two dose groups and then to active drug or placebo. Patients in all groups came to the infusion clinic at the Center for Conquering Cancer on the same day each week. They infused via an intravenous line for approximately 1 hour of time each week for 6 weeks.

This study was approved by the Center for Conquering Cancer IRB review board on December 11, 2011. Data from the study was kept on a laptop in the study office.

*MEASURES*

Before treatment, patients had MRI scans to measure size of their tumors. Physical exam findings and results of blood tests included CBC, chem-7 (BUN, creatinine, CO2, glucose, serum chloride, serum potassium, and serum sodium), liver panel, and cholesterol.

Adverse events (AEs) and use of concomitant treatments were reported by patients at study visits throughout the trial. Study physicians determined the AEs intensity and relationship using pre-defined standard descriptors.

*STATISTICAL PROCEDURES*

The sample size of this study was based upon the findings of previous placebo-controlled study in patients with SCC head and neck cancer.[7](#_ENREF_7) It was estimated that the response rate in the placebo group might be approximately 15 percent leading to a response rate of 30 percent in the active drug group. It was also assumed that the placebo patients randomized to each cohort could be pooled for the analyses of efficacy, so that the overall allocation ratio for the 4 study treatments would be 1:1:1:1. Give these assumptions, 70 patients randomized to each treatment group would have 80 percent power to detect an increase of 30 percent in the response rate with R-837A. This calculation meant that 210 patients would be necessary to be randomized to the 4 treatment groups (140 in each dose cohort, and 70 in each treatment group).

The efficacy endpoint was a 5 percent or more reduction of primary and secondary tumors at the end of the study period. Other endpoints included the subject choosing to leave the study, subject disqualification for pursuing concomitant treatment, or patient not finishing the trial, or death.

A –repeated measures MANOVA was performed with membership in either the placebo or treatment condition (.25 cc or .50cc) as the independent variable and the dependent variables were number of tumors and reduction in tumor size). An examination of the univariate analyses found significant differences between placebo and treatment groups with regard to the number of tumors present at study completion (p =0.000). Significant differences were found across the three groups (p=0.000) on tumor size at study completion. Pairwise comparison of means found that the .50 cc group had significantly smaller tumors at study completion than did the placebo and .25cc group.

Results

A total of 346 patients were screened over 3 months at the Center for Conquering Cancer in San Antonio, Texas. One hundred thirty six did not meet screening standards of number of rounds of therapy undergone, mental health, or agreeing not to pursue concomitant treatment. Of those, 210 were randomized into one of the three arms of the study. Of the 210, 155 (73.8 percent) completed the study. The 26.2 percent who did not complete the study fell out for several reasons including not completing the protocol, violating protocol by pursuing other treatment, choosing not to continue because of side effects, or failure to complete due to death or other severe reaction. Table 1 shows the number of subjects who began each arm and the number that actually completed the study.

TABLE 1: Recruited/Completed by Trial Arm

|  |  |  |  |
| --- | --- | --- | --- |
| Group | Placebo | 0.25cc | 0.50cc |
| Began Study/Completed | 70/68 | 70/56 | 70/31 |

Of patients who completed the study, the mean number of tumors discovered on MRI full-body scan increase by 1.8 on placebo, by 1.4 on 0.25cc, and by 0.9 on 0.50cc (see Table 2). A MANOVA calculation produces a *p-value* of 0.001, suggesting high significance (see Figure 1).

TABLE 2: Reduction in Numbers of Tumors

|  |  |  |  |
| --- | --- | --- | --- |
| Group | Placebo (n=68) | 0.25cc (n=56) | 0.50cc (n=31) |
| Average Number of Tumors at Start | 4.3 | 4.4 | 4.2 |
| Average Number of Tumors at Finish | 6.1 | 5.8 | 5.1 |
| Average Change from Start to Finish | +1.8 | +1.4 | +0.9 |

FIGURE 1: MANOVA on Table 2 Results

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | SS | Df | MS | F | P |
| Between | 177.47 | 2 | 8.873 | 7.725 | 0.001 |
| Within | 174.586 | 152 | 1.149 |  |  |
| Total | 192.333 | 154 |  |  |  |

Subjects on R-837A also experienced a reduction in the size of their primary tumor. As reported in Table 3, those subjects on the placebo actually experienced tumor growth averaging 0.6mm while those on 0.25cc experienced a reduction of 0.6mm and those on 0.50cc had tumor reduction of 0.9mm. MANOVA results show a high level of significance with a *p-value* of less than 0.000.

TABLE 3: Reduction in Size of Primary Tumor

|  |  |  |  |
| --- | --- | --- | --- |
| Group | Placebo (n=68) | 0.25cc (n=56) | 0.50cc (n=31) |
| Average Size of Primary Tumor at Start | 6.6mm | 6.7mm | 6.5mm |
| Average Size of Primary Tumor at Finish | 7.2mm | 6.1mm | 5.6mm |
| Average Change from Start to Finish | 0.6mm | -0.6mm | -0.9mm |

FIGURE 2: MANOVA on Table 3 Results

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | SS | Df | MS | F | P |
| Between | 66.986 | 2 | 33.493 | 149.252 | 0.000 |
| Within | 34.109 | 152 | 0.224 |  |  |
| Total | 101.095 | 154 |  |  |  |

Discussion

In this study, R-837A was tested in two dosing arms, 0.25cc and 0.50cc delivered via an intravenous infusion. A third arm of the study used a placebo group to serve as control. Of those subjects who completed the trial, the higher dose of R-837A was statistically associated with a lower mean number of tumors by nearly an entire metastatic tumor and a reduction in the size of the primary tumor. This statistically significant result suggests that an even higher dose may have led to greater efficacy, a hypothesis that will need to be tested in another study.

That 26.2 percent of subjects did not complete the study suggests that more rigorous screening is necessary for determining who will benefit for this program. Future studies should examine the criteria that define who makes and who does not make a strong candidate for this drug. Effective dosing is associated with higher rates of side effect and drop out. This is an area that should be studied further.

There are several limitations to this study. One, the study was conducted at only a single institution. Two, the exclusion criteria were not as extensive as they needed to be. Third, a larger sample size may have been necessary to properly power the study.

Conclusion

This study demonstrated the efficacy of R-837A for safely reducing the size and number of tumors in patients with advanced squamous cell carcinoma. Although more studies are necessary, we suggest that a larger phase 3 clinical trial be conducted to further determine the efficacy of R-837A.

References

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1. Note. Much of the design for this study and language in this mock paper is derived and quoted from Portenoy RK, et al (2012). Nabiximols for Opiod-Treated Cancer Patients with Poorly-Controlled Chronic Pain: A Randomized, Placebo-Controlled, Graded-Dose Trail. The Journal of Pain 13(5 May): 438-449. [↑](#endnote-ref-1)